Target Therapies in Systemic Lupus Erythematosus: Current State of the Art

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Abstract: Systemic lupus erythematosus (SLE) is a complex autoimmune disease of unknown etiology and limited available therapeutic options frustrating both clinicians and patients. However, recent advances in the understanding of disease mechanisms have given rise to numerous studies on specific approaches to SLE treatment. The purpose of this review is to explain the rationale for new treatments and results of the first clinical studies. We will focus on agents which deplete B cells (anti-CD20, anti-CD22), block cytokines (TNF α, Il 6), inhibit B/T cells interaction (CTLA-4Ig, anti-CD40L), or are even expected to reconstruct physiologic immunotolerance. Although preliminary results seemed promising, two randomized clinical trials with rituximab (EXPLORER and LUNAR study) failed to prove efficacy. Data analysis continues to explain the reasons. Trial design, subject population, limitations of the outcome measure instrument and site qualification have been questioned. Future studies are likely to focus on specific organ involvement or treatment combinations with other immunosuppressive agents.

Keywords: B cells, systemic lupus erythematosus, rituximab, epratuzumab, BLyS, LJP 394, anti-cytokine therapy, monoclonal antibodies, clinical trials.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune inflammatory disease, which mainly affects women (ratio 9:1), mostly during their childbearing years. The disease is heterogenic, with a wide spectrum of symptoms, internal organ involvements and autoantibody profiles. Currently used therapies, corticosteroids and non-specific immunosuppressant medication, seem to be unsatisfactory, due to lack of efficacy and a number of side effects, including: serious infections [1], increased risk of malignancies [2], secondary infertility after cyclophosphamide therapy [3] or Cushing's syndrome. During the past 10 years, biologic agents that target cytokines or immunocompetent cells proved to be an effective and safe strategy for the treatment of rheumatoid arthritis (RA) and ankylosing spondylitis [4]. This clinical experience, along with progress in understanding the pathogenesis and identifying the abnormalities of immune response, led to the discovery of potential targets for modern SLE treatment [5]. New agents directly react with hyperactive B lymphocytes, modulate B and T cell interaction or inhibit cytokine activity. On the other hand, despite extensive research, no new treatment has yet been approved for SLE. In this article we reviewed the rationale for the use of new drugs in SLE, and results of clinical studies published to date.

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PATHOPHISIOLOGY

B Lymphocytes

B lymphocytes are essential cells constructing the humoral part of human immunity. Mature B cells are clearly differentiated from other lymphocytes by their synthesis and display of membrane-bound immunoglobulin (antibody) molecules, which serve as receptors for antigens. Each of the approximately $1.5x10^5$ molecules of antibody on the membrane of a single B cell has an identical antigen-binding site. Molecules expressed on the membrane of mature B cells are crucial for B cell recognition and function and currently, some of them are believed to represent targets for modern therapies in autoimmune diseases (Fig. **1**):

- The B cell receptor (BCR) is a membrane-bound immunoglobulin and serves as a receptor for antigens.
- CD20 is a typical marker molecule for B cells and their precursors.
- CD22 is constitutively associated with BCR in resting B cells. It interacts with CD45R, serves as coreceptor and increases activation of T cells.
- B220 (a form of CD45) is frequently used as a marker for B cells and their precursors. However, it is not expressed uniquely by B-lineage cells.
- Class II MHC molecules permit the B cell to function as an antigen-presenting cell (APC).
- CR1 (CD35) and CR2 (CD21) are receptors for certain complement products.

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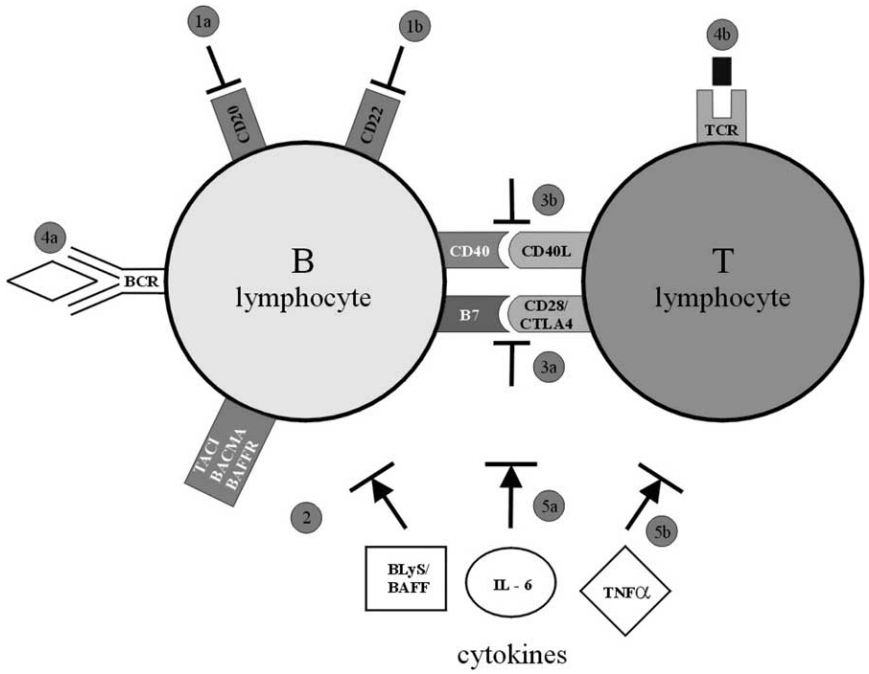

Fig. (1). Novel target therapies in systemic lupus erythematosus.

B cell depletion therapies: anti-CD20 antibodies, rituximab (1a), anti-CD22 antybodies, epratuzumab (1b), antagonists of B cell activation (2). Inhibitors of B/T cells interaction: abatacept (3a), IDEC131 (3b). Tolerance inductors: abetimus sodium (4a), edratide (4b). Cytokines blockers: tocilizumab (5a), TNFα inhibitors (5b).

- FcγRII (CD32) is a receptor for IgG, a type of antibody.
- B7-1 (CD80) and B7-2 (CD86) are molecules that interact with CD28 and CTLA-4, important regulatory molecules on the surface of various types of T cells, including Th cells.
- CD40 is a molecule that interacts with the CD40 ligand on the surface of helper T cells. In most cases this interaction is critical for the survival of antigen-stimulated B cells and for their development into antibody-secreting plasma cells or memory B cells.

Maturation of B cells takes place in the bone marrow and is regulated by complex mechanisms, which include cytokines produced by immunocompetent cells of the bone marrow stroma, such as activated T cells and macrophages, and the controlled induction of cell death (apoptosis).

After B cells leave the bone marrow, their activation, proliferation and differentiation in the periphery requires an antigen. Antigen-driven activation and clone selection of naïve B cells leads to the generation of plasma cells and memory B cells. In the absence of antigen-induced activation, naïve and peripheral B cells have a short life-span, dying within a few weeks by apoptosis.

Activation of Antigen-Presenting Cells (APC) and T Helper (Th) Cells

Activation of both the humoral and cell-mediated branches of the immune response requires cytokines produced by Th cells. The process of Th cell activation is precisely regulated in order to prevent an inappropriate T-cell response to self-components. To keep Th cells under strict regulation, their activation requires recognition of antigens displayed together with class II MHC molecules on the surface of APCs. These specialized cells, which include macrophages, B lymphocytes, and dendritic cells, are distinguished by two properties: expression of class II MHC molecules on their membranes, and ability to deliver a co-stimulatory signal that is necessary for Th-cell activation.

The B cells are considered as the most potent antigen-presenting cells, due to their antigen-binding capacity as well as their ability to directly contact the Th cells. After the antigen is attached to a membrane-bound immunoglobulin receptor on B cells, the whole complex is internalized by endocytosis and processed into peptides. Antigen binding initiates up-regulation of a number of cell-membrane molecules, including class II MHC molecules and the B7 co-stimulatory ligands, which enhances the ability of the B cell to function as an antigen-presenting cell in Th cell activation. Since a B cell recognizes and internalizes antigen specifically, *via* its membrane-bound immunoglobulin, a single B cell is able to present antigen to Th cells at antigen concentrations that are 100 to 10,000 times lower than those required for presentation by macrophages or dendritic cells.

Once a Th cell recognizes a processed antigenic peptide displayed by a class II MHC molecule on the membrane of a cell, the two cells interact to form a T-B conjugate. This direct contact not only leads to the directional release of Th cell cytokines, but also to the up-regulation of the CD40 ligand (CD40L), a membrane protein that interacts with CD40 on B cells to provide an essential signal for T-cell-dependent B cell activation. CD40 controls B cell prolifera-

tion and apoptosis. Interaction of CD40L with CD40 on the B cell delivers a second signal to the B cell that, together with the signal generated by membrane-bound immunoglobulin receptor (first signal), leads to B cell activation and proliferation.

Stimulated B cells are able to proliferate, however they fail to differentiate unless cytokines are present, including IL-2, IL-4, IL-5, as well as BLyS (B lymphocyte stimulator) and APRIL (a proliferation inducing ligand), the two newly discovered molecules. The signals provided by cytokines maintain B cell proliferation and induce differentiation into plasma cells, induce class switching, affinity maturation and lead to the development of memory B cells.

B cells play a crucial role in the pathology of SLE. Studies have documented [6] abnormal B cell proliferation, maturation, and a prolonged life-span of autoreactive clones as well as autoantibody production, along with immune deregulation, and tolerance breakdown [7].

The following section will detail novel therapeutic agents based on immunologic abnormalities involved in the pathogenesis of SLE (Table **1**).

B CELL DEPLETION THERAPY

Anti-CD20 (Rituximab)

CD20 is a lymphocyte B restricted surface molecule, expressed from pre-B to memory B cells. Despite intensive studies, its function remains a puzzle. CD20-knockout mice do not represent specific phenotype abnormalities and have normal immunologic response. CD20 has no known natural ligand [8]. It is a phosphoprotein with a structure of 4 transmembrane regions and an amino-acid extracellular loop. According to structural homologies, it is supposed that CD20 may have a calcium channel function.

Rituximab is the first chimeric, mouse-human monoclonal antibody which was approved in 1997 for treatment of indolent CD20 non-Hodgkin's lymphoma and recently for RA. Administration of the CD20-specific antibody results in death of B cells achieved by antibody-dependent cell-mediated cytotoxicity, complement–mediated lysis or apoptosis.

Rituximab influences homeostasis and improves the disturbances in peripheral B cells characteristic for active SLE [9]. After effective B cell depletion, on reconstitution period, naive B cell lymphopenia, expansion of a CD27-, IgD- (double negative) population, and expansion of circulating plasmablasts are significantly decreased. The frequency of autoreactive memory B cells decreased 1 year post-treatment, despite persistent elevation of dsDNA titer. However the magnitude, duration and consequences of depletion therapy in SLE have not been completely elucidated. Long-term follow-up (mean duration 41 months) has shown a delayed recovery of memory CD27+ B cells in peripheral blood and lymphoid tissue after rituximab administration [10]. Authors suggested that a reconstitution profile dominated by memory B cells, as opposed to transitional B cells, might represent a marker to guide re-treatment with rituximab. Moreover, the fact that in SLE patients reconstituted B cells are predominantly memory B cells might be specific for the disease. This is in unlike RA and lymphoma patients, where transitional and naïve B cells dominate.

Table 1. New Therapy for Systemic Lupus Erythematosus

Mechanism of action	Agent	Findings in human studies
B-cell depletion	Anti-CD20 (Rituximab)	Clinical benefits in open label trials, well tolerated, concerns regarding PML cases and HACAs induction, RTC failed to prove treatment efficacy
	Anti-CD22 (Epartuzumab)	Well tolerated, tendency for clinical improvement in open-label study, two studies terminated due to interruptions in medication supply.
Inhibition of B cell stimulation	Anti-BLyS (Belimumab)	Safety confirmed in phase III study with observation prolonged up to 3 years, efficacy in limited, seropositive SLE patients, phase III study currently ongoing.
	TACI-IgG (Atacicept)	Well tolerated, decrease of dsDNA titer, RTC under way.
Inhibition of T cell - B cell interaction	CTLA-4Ig (Abatacept)	Early studies in human SLE currently ongoing.
	Anti-CD40ligand (IDEC131, BG9588)	In phase II studies efficacy end-points not met, trials terminated prematurely due to thromboembolic events.
Tolerance induction	B cell tolerogen (LJP 394)	Good safety profile, significant reduction of dsDNA, not proved renal flares reduction, phase III/IV study terminated after interim analysis due to lack of efficacy
	T cell tolerogen (Eratide)	Well tolerated in preliminary studies
Cytokines	Anti-TNF (Infliximab)	Clinical benefits in open-label study, RTC currently ongoing. Series of drug induced lupus in RA patients after TNF blockade.
	Anti-IL6 receptor (tocilizumab)	Well tolerated in early phase studies, RTC in cutaneous SLE currently ongoing.

A case report gave an account of successful treatment of SLE-related life-threatening autoimmune hemolytic anemia, which did not respond to methylprednisolone pulse therapy, intravenous immunoglobulin and cyclosporine A. The authors administered two rituximab 375mg/m^2 infusions (1 week apart). The patient's condition improved on the 5th day after the second infusion and she remained disease free up to 7 months after treatment [11]. Further uncontrolled clinical studies have shown promising results [12-21]. The percentage of responding patients was high, independent of indications, medication regimens and tools used for assessment (Table **2**).

Rituximab was well tolerated although antibodies against rituximab (HACAs) were detected at a significantly higher rate then in lymphoma patients. The presence of HACAs was associated with disease activity at baseline, reduced B-cell depletion and African-American ancestry, which suggests that chimeric antibodies can be more immunogenic in more active SLE. Notably, the proportion of patients on a low rituximab dose in the open studies was relatively high, so the relationship may be not universal for the disease. Later on, was reported that B cell depletion varies with FcγRIIIa allele polymorphism [22].

Safety data on rituximab in humans are mainly based on experience in non-Hogkin's lymphoma (more than 1 000 000 patients exposed) and RA studies [23]. The most frequent side effects are infusion reactions, reduced by intravenous administration of corticosteroids. Serious infections have been observed with a frequency similar to other biologicals. Concerns arise in connection with a report on 2 cases of progressive multifocal leukoencephalopathy (PML) in patients with severe SLE [24]. There have been 26 other reports of PML in SLE patients who were not using rituximab, but were on immunosuppressive treatment. The exact role of rituximab in the development of PML is unclear, as humoral immunity seems to be of little importance in the latency and reactivation of the JC virus [25]. Therefore caution must be exercised with the implementation strategies profoundly influencing the immune system.

Presented data merited the staging of a randomized clinical trial for rituximab. In the meantime, rituximab is used off-label for the treatment for autoimmune disease in clinical practice [26]. The manufacturer estimated that 10 000 SLE patients had received the drug. The randomized, double-blind Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial tested the efficacy and safety of rituximab versus placebo in patients with moderately to severely active extrarenal SLE [27]. The trial enrolled 257 patients with significant disease activity (81% entered with 1 ≥ BILAG A score or 3 ≥ BILAG B score). Patients were maintained on the background treatment throughout the trial and both arms were given a steroid initiation for immediate control of disease activity. Primary endpoints were clinical response at week 52 assessed using the British Isles Lupus Assessment Group (BILAG) organ system score, which scores patients based on the need for alterations and intensification of therapy. A treatment failure definition included 1 new BILAG B score after 6 months, which is very rigorous. No differences were observed between placebo and rituximab in the efficacy end-points. In both groups significant improvement was observed by day 28 due to initial steroid treatment and was maintained after dose taper. This suggests that benefit of initial steroid therapy was maintained by background immunosupression without any additive rituximab influence. This study accomplished some important

Table 2. Open-Label Studies of Rituximab in Patients (n≥10) with Systemic Lupus Erythematosus

Year	Pts' characteristics	N	Treatment regimen	Main results	References
2004	Mild-moderate SLE	17	Rituximab:1x100mg/m²(low dose); 1x375mg/m² (intermediate dose); 4 weekly doses of 375mg/m² (high dose)	B cell depletion dose independent, response for arthritis and mucocutaneus symptoms, high proportion of HACAs	[12]
2005	Refractory SLE, long-term follow-up (24 months)	24	Protocol 1: rituximab 2x500mg, cyclophosphamide 750mg iv, oral prednison 30-60mg; protocol 2: rituximab 2x1000 mg (every 2 weeks), cyclophosphamide 750mg iv, methylprednisolon 250mg iv	Significant clinical improvement in BILAG (global and organ specific), no differences between protocols, 7 patients relapsed and were re-treated	[14]
2005	Active lupus nephritis	10	Rituximab 4 weekly infusions 375mg/m²	Improvement in 8 patients, 4 with complete remission, sustained 12 months	[17]
2007	Refractory SLE	11	Rrituximab 4 weekly infusions 375mg/m², cyclophosphamide 1x500mg iv	BILAG improvement, 7 patients relapsed after 12 months	[16]
2007	Active or refractory SLE	14	Rituximab 4 weekly infusions 500 mg or 2 infusions 1000mg every 2 weeks	9/14 clinical response in BILAG score	[19]
2008	Lupus flare not responding to conventional treatment	16	Rituximab 4 weekly infusions 375mg/m², cyclophosphamide 500mg/m²	15/16 clinical improvement in BILAG score	[20]

tasks: enrolling demonstrably ill patients, strict background therapy rules, clear definition of efficacy end-points, sensitive treatment failure cut-off. Negative results suggest that the disease is more heterogenous in biology and not uniquely B-cell driven. A beneficial effect of rituximab was observed only in the African American and Hispanic subgroups, i.e. populations which are more refractory to standard treatment and possibly more B cell dependent. Further evaluation of patient subsets and biomarkers continues, and may help to improve design of future studies. Moreover, the LUNAR trial failed to show any benefit of rituximab in lupus nephritis. Results of this trail are not yet available for analysis. The disappointing outcomes of randomized trials in the context of promising case series lead to doubts and concerns about the design of the trials themselves [28].

Anti-CD22 (Epratuzumab)

Another B cell restricted target is CD22, a 135-kD surface glycoprotein, which is a specific adhesion molecule that regulates B cell activation and interaction with T cells [29-31]. CD22 has 7 extracellular domains and is rapidly internalized when cross-linked with its natural ligand, producing a potent co-stimulatory signal in primary B cells [32]. Epratuzumab is a monoclonal IgG1 antibody (IMMU-103) 90-95% of human origin, which reduces the potential for immunogenicity, even in case of multiple injections.

Initial clinical experience with epratuzumab includes patients with non-Hodgkin's lymphoma or other B cell malignancies, who received 4 consecutive weekly infusions at doses ranging from 120-1000mg/m^2/week, with weekly premedication by oral acetaminophen and diphenhydramine [33,34]. There were no safety concerns noted in the study. After the 4th weekly infusion, epratuzumab blood levels increased in a dose-dependent manner, and the drug remained in circulation with a half-life of 19 to 25 days, consistent with the half-life of human IgG. Therefore, for the initial SLE study, a longer dose interval was selected with a biweekly dosing schedule [35]. This open-label study involved 14 patients with stable, moderately active SLE (BILAG global score 6-12). Patients received 360mg/m^2 of epratuzumab intravenously every 2 weeks for 4 doses (standard premedication, without steroids). The patients were monitored for 6 months post-treatment, with the following evaluations: safety profile, disease activity (BILAG score), drug pharmacokinetics, B and T cells, immunoglobulins, and human anti-epratuzumab antibody titers (HAHA). Therapy was safe and well tolerated, with evidence of clinical improvement justifying further study. HAHA analysis gave no evidence of immunogenicity, with post-treatment values either not detected or not different from baseline. After treatment, in contrast to rituximab, B cell levels decreased by 35%. T cells and immunoglobulin levels did not change. Although patients clinically improved, no reduction of ANA or dsDNA occurred. Authors suggested that epratuzumab could potentially mediate direct pharmacological effects by negative regulation of hyperactivity of a certain B cell subset, moreover that epratuzumab inhibited the proliferation of B cells from patients with SLE but not normal B cells, regardless of culture conditions [36]. Results supported the case for further randomized clinical trials; unfortunately two studies were prematurely terminated due to interruptions in medication supply [37].

B-LYMPHOCYTE STIMULATOR ANTAGONISTS

Anti-B-Lymphocyte Stimulator (Anti-BLyS, LymphoStat-B Antibody, Belimumab)

The B-lymphocyte stimulator (BLyS) is a member of the TNF ligand family expressed on cells of myeloid origin, including monocytes, macrophages and dendritic cells. The predominant active form of BLyS is a homotrimer consisting of three 152 amino acid peptide chains. It is supposed that only the soluble form of BLyS is biologically active. BLyS binds to three membrane receptors: TACI (transmembrane activator and CAML-interactor), BCMA (B-cell maturation antigen) and BAFF-R (B-cell Activating Factor belonging to TNF factor family), which expression is highly specific for B lymphocytes.

Studies on animal models show that mice genetically deficient in BLyS display profound global reductions in mature B cells, baseline serum IgG levels and response to T cell dependent and T cell independent antigens. In murine SLE models, BLyS overproduction leads to elevated titers of autoantibodies, including dsDNA and circulating immune complexes.

Human experimental studies revealed abnormal activity and elevation of BLyS in the sera of SLE patients. The following patterns were found: approximately 20-30% subjects tested abnormal in single time-points [38,39]; serially tested patients had abnormal results persistently in 25% and intermittently in a further set of 25% [40]. These data support the hypothesis that BLyS inhibition may be beneficial [41].

Belimumab, a fully human IgG1 antibody that binds to soluble BLyS, inhibits its biological activity [42]. A phase I clinical trial (70 lupus patients enrolled) documented safety of the drug.

A phase II, randomized, double-blind, dose-ranging study of belimumab in SLE with mild and moderate disease activity confirmed that therapy was safe, but the efficacy endpoints were not met [43]. Belimumab was administered intravenously initially on days 0, 14, 28 and then every 28 days. SELENA SLEDAI and SELENA SLEDAI Flare Index were used for activity assessment. At week 24 and 52 there was no significant improvement in disease activity except for patients who were ANA or dsDNA positive at baseline. A further phase III RCT in seropositive subjects is currently ongoing.

TACI-IgG (Atacicept)

APRIL (A proliferation inducing ligand), a "cousin" of BLyS, belongs to the same TNF ligand family, which shares homology with BLyS and binds to two of three receptors, TACI and BCMA, but not to BAFF-R [44]. Although data regarding the role of APRIL in autoimmunity are conflicting, some authors confirmed APRIL elevation in sera of SLE patients when compared with healthy individuals and patients with rheumatoid arthritis [45].

Atacicept (TACI-IgG) is a recombinant fusion protein comprising the extracellular domain of the TACI receptor combined with the human IgG1 Fc domain. Atacicept blocks B lymphocyte stimulation by both BLyS and APRIL. Transgenic mice that express atacicept have few mature B cells

and reduced concentrations of immunoglobulin [46]. Furthermore treatment of lupus-prone female mice with atacicept delays the development of proteinuria and prolongs survival [47]. In published results of phase Ib, dose escalating (0.3 mg/kg to 9 mg/kg sc) trial in patients with mild to moderate lupus, atacicept administered subcutaneously was well tolerated [48]. Although the study was not powered to determine the impact on disease activity, the SELENA SLEDAI scores and dsDNA titer decreased compared to baseline. These preliminary results will be investigated in a phase II/III clinical trials.

T CELL/B CELL INTERACTION THERAPIES

In search of an alternative target to B cell depletion, researchers shifted their attention to costimulatory signaling pathways. T cell costimulation is critical for normal immune function and for the pathogenesis of some autoimmune diseases. For the initiation of T cell dependent B cell response, the T cell requires two distinct signals. The first signal consists of the binding of the T cell receptor (TCR) to the antigen in the context of class II major histocompatibility antigens (MHC II). The second signal consists of interactions between receptor-ligand pairs on T cells and antigen presenting cells (APCs) [49]. Research focused on two main costimulatory pathways of inhibition: the CD28/CTLA4: CD80 or CD86 and the CD40:CD40L.

Cytotoxic T-Lymphocyte-Associated Antigen-4 Immunoglobulin (CTLA-4Ig)

CTLA-4 is a protein naturally present on activated T cells. It binds to CD80 or CD86, and simultaneously transmits an inhibitory signal to the T cell, thereby blocking proliferation. Abatacept is a recombinant fusion protein composed of the extracellular domain of CTLA-4 fused to an Fc part of human IgG1, modified to prevent complement activation. Abatacept competes with CD28 for biding to CD80 and CD86.

Several clinical trials proved abatacept to be safe and effective in patients with RA, even with inadequate response to TNF blockers [50, 51]. Pre-clinical studies in a murine model of SLE treated with abatacept show increased survival, decreased levels of dsDNA and proteinuria. An extremely effective combination in mice was that of abatacept with cyclophosphamide in the treatment of early and advanced nephritis [52]. These preliminary experimental data seem very promising. Results in human lupus treatment are eagerly awaited.

Anti-CD40 Ligand (Anti-CD40L, Anti-CD154, IDEC-131)

Abnormal expression and deregulation of CD40L has been associated with SLE [53]. In sera of active lupus patients, the absolute number of CD40L positive T cells and levels of the soluble form of CD40L were increased when compared with healthy controls. Prolonged anti-CD40L treatment in nephritic mice increased survival and reduced severity of renal disease.

IDEC-131 is a humanized monoclonal antibody against CD40L, comprising human γ1 heavy chains and human κ light regions. In a phase I trial IDEC-131 was well tolerated in 23 patients with SLE, at single doses of 0.05 to 15.0 mg/kg given intravenously [54]. In a phase II, double blind, placebo controlled study, which enrolled 85 patients with mildly or moderately active SLE, treatment was safe but, compared to placebo, no efficacy was demonstrated (by the SLEDAI or any multiple measures) [55]. Further studies with this costimulatory pathway inhibition had to be stopped due to thrombotic events, which occurred with a different anti-CD40L antibody (BG9588) [56]. Thromboembolic events were the most unexpected, that several studies have identified presence of CD40L on the surface of activated platelets, and found that it may play role in triggering an inflammatory reaction in endothelial cells [57].

TOLERANCE INDUCTION

Abnormal immune response to self-antigens and own tissues is a hallmark of SLE. Restoration of tolerance to autoantigens is another therapeutic option. Tolerogens are synthetic molecules that bind to and cross-link autoantibodies, leading to anergy (functional inactivation) or deletion of autoreactive B or T cells.

B-Cell Tolerogen (LJP 394, Abetimus Sodium)

Anti-double-stranded DNA (anti-dsDNA) antibodies are the best known SLE serologic markers. The increase in anti-dsDNA antibody levels is associated with higher risk of renal flare [58]. LJP 394, also known as abetimus sodium, is a synthetic compound of four deoxynucleotide sequences bound to a triethylene glycol backbone. Structurally, >97% of LJP 394 is composed of oligonucleotides derived from dsDNA and would be expected to interact only with proteins capable of recognizing of dsDNA [59]. Experience with abetimus sodium in human SLE demonstrated significant and sustained reduction in anti-dsDNA antibodies as well as safety of the drug, but failed to prove clinical benefits and significant reduction of renal flares. However LJP 394-treated patients had a longer time to institution of high-dose corticosteroids and/or cyclophosphamide and required fewer treatments comparing with the placebo group [60]. A phase IV trial, which was supposed to recruit over 800 patients with a history of lupus nephritis was prematurely terminated due to lack of clinical efficacy revealed by interim analysis.

T-Cell Tolerogen (TV-4710)

TV-4710 (Edratide) is a peptide derived from the immunoglobulin Vh region of human anti-dsDNA antibody. Administration of the peptide is supposed to induce regulatory T cells, which suppress autoreactive Th cells. In animal models edratide has been shown to reduce proteinuria and immune complexes in the kidneys. It is now presumed to be a possible adjuvant therapy in human SLE.

ANTI-CYTOKINE THERAPIES

Although there are controversies regarding cytokine networks in SLE, as most of those tested have been found to be abnormal [61], these messengers of immune cells are another potential target for therapeutic intervention.

Anti-TNF-α Therapies

TNF-α is a potent inflammatory cytokine produced by a variety of cell types, including monocytes, macrophages, T

and B cells. It stimulates the production of other inflammatory mediators such as IL-1, IL-6, IL-8, and granulocyte-monocyte colony-stimulating factor (GM-CSF). TNF-α antagonists, infliximab (a chimeric IgG1 antibody), etanercept (a fusion protein consisting of two recombinant TNF receptors and Fc part of human IgG1) and adalimumab (a completely humanized antibody) decrease disease activity and prevent damage in RA. However these data cannot be directly extrapolated to SLE. Clinicians are even reluctant to use anti-TNF-α agents in SLE, because some patients with RA or Crohn's disease treated with infliximab developed antinuclear antibodies, anti-dsDNA antibodies and lupus-like disease [62,63]. On the other hand TNF-α affects a variety of cells important in SLE [64]. Animal models confirm that TNF plays a role in the inflammatory response in the kidney [65]. An open-label study of infliximab (4 x 300 mg infusions) in addition to baseline immunosuppressive therapy in 6 patients with mild-to-moderate lupus, 4 with lupus nephritis, gave promising results [66] with significant decrease of proteinuria and resolution of arthritis. A trial with TNF-α blockade in membranous nephritis is currently underway.

IL-6 Antagonist

IL-6 is a pleiotropic cytokine secreted by monocytes, T cells, B cells and mesangial cells. It stimulates B cell maturation and immunoglobulin production. In synergy with other cytokines, it induces T cell growth and differentiation to cytotoxic lymphocytes, supports stem cell maturation and neutrophil activation [67] and may play a role in SLE pathogenesis [68,69]. Tocilizumab is a humanized monoclonal antibody, which targets the IL-6 receptor α chain and prevents binding of IL-6 to its receptor. In one trial, 14 patients with mild-to-moderate SLE received tocilizumab 2-8 mg/kg over two weeks. On treatment significantly decreased acute phase reactant, activated B cells and memory B cells. Clinical benefits of this therapeutic approach have to be elucidated. Data from RA studies show that tocilizumab induces a number of laboratory abnormalities: neutropenia, increase of liver enzymes, cholesterol and triglyceride concentrations. Especially the clinical significance of lipid abnormalities has to be determined, as accelerated atherosclerosis and cardiovascular disease are among the main causes of death in SLE patients [70].

CONCLUSION

Caring for the patients with systemic lupus erythematosus is a significant challenge. Only three drugs – corticosteroids, hydroxychloroquine and low-dose aspirin – are approved by FDA for SLE treatment. New therapies, which specifically target different cells and cytokines involved in the pathogenesis of the disease, offer promise for more effective treatment. However, it is important to note that data, which confirm their efficacy, came mostly from open label studies or early phases of clinical trials with limited numbers of patients. Life-threatening complications after the administration of anti-CD28 monoclonal antibodies to healthy volunteers [71], or unusual adverse events as PML, implicate the same consideration. Only large controlled clinical trials can establish the safety and efficacy of new agents in SLE treatment. However, the recently announced disappointing results of the EXPLORER and LUNAR trials, raise concerns about the future of lupus studies, which are upheld by the postponement by Roche of studies on a humanized anti-CD20 antibody (ocrelizumab).

The lupus research community strongly advocates continuing research but calls for more attention to the design of the trials themselves, as well as appropriate selection of cases and centers. Disease activity scores allow a comparison in SLE patients whose disease affects different organ systems with fluctuating intensity. However, they only become good tools in the hands of experienced clinicians who are able to differentiate irreversible damage from active disease. Recently novel responder indices have been proposed to improve efficacy assessments [72]. Other questions are how intensive background treatment should be in patients with active disease and what duration of follow-up is needed for benefits of new drugs to become apparent. An alternative way of conducting research is to define various biological mechanisms and genetic backgrounds, which explain the varied manifestations of diseases and predict response to treatment allowing for more individualized or organ-specific therapies. Finally, the possibility exists that new target therapies will be more effective in refractory disease when combined with cyclophosphamide.

ABBREVIATIONS

SLE	=	Systemic lupus erythematosus
RA	=	Rheumatoid arthritis
SLAM	=	Systemic Lupus Activity Measure
SLEDAI	=	Systemic lupus erythematosus disease activity index
APC	=	Antigen-presenting cell
CD40L	=	CD40 ligand
BLyS	=	B-lymphocyte stimulator
APRIL	=	A proliferation inducing ligand
anti-dsDNA	=	anti double stranded DNA antibodies
ANA	=	Anti-nuclear antibodies
HACAs	=	Antibodies against rituximab
BILAG	=	British Isles Lupus Assessment Group
PML	=	Progressive multifocal leukoencephalopathy
HAHA	=	Human anti-epratuzumab antibody titers
TACI	=	Transmembrane activator and CAML-interactor
BCMA	=	B-cell maturation antigen
BAFF-R	=	B-cell activating factor belonging to TNF factor family
TCR	=	T cell receptor
CTLA-4Ig	=	Cytotoxic T-lymphocyte-associated antigen-4 immunoglobulin

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Received: April 16, 2010 Revised: June 14, 2010 Accepted: June 19, 2010